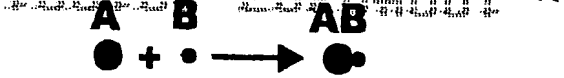
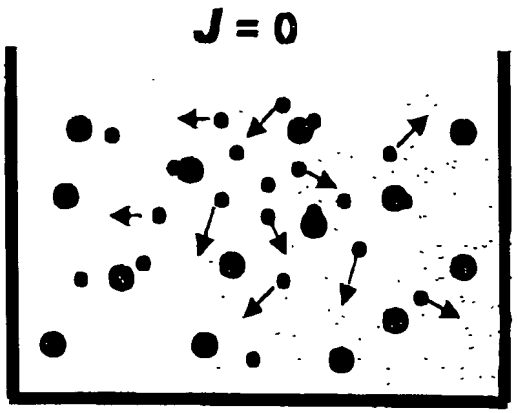
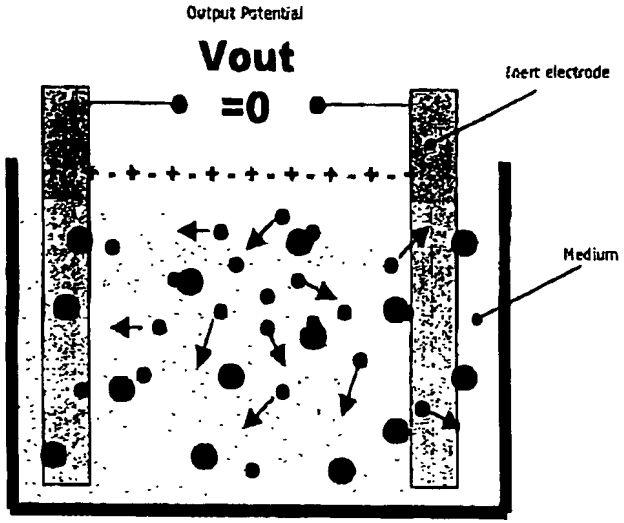


J : Current Density of B

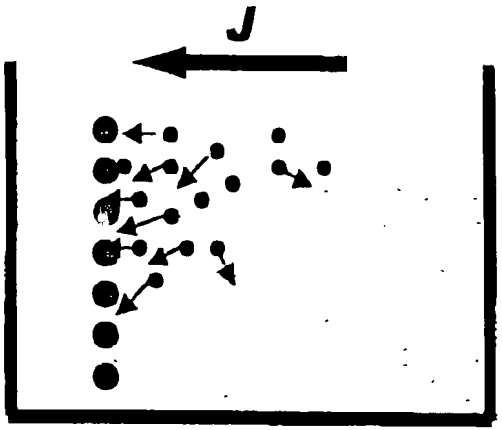
1.1

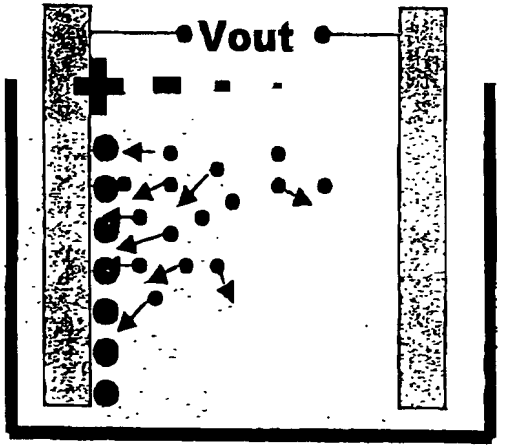




1.1) If A and B are both free in the medium no net transient gradient of molecules (current density) is created.

1.2

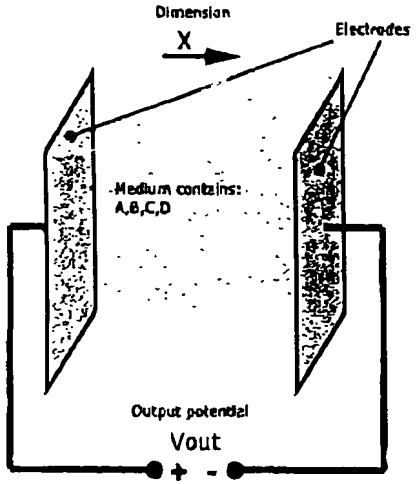


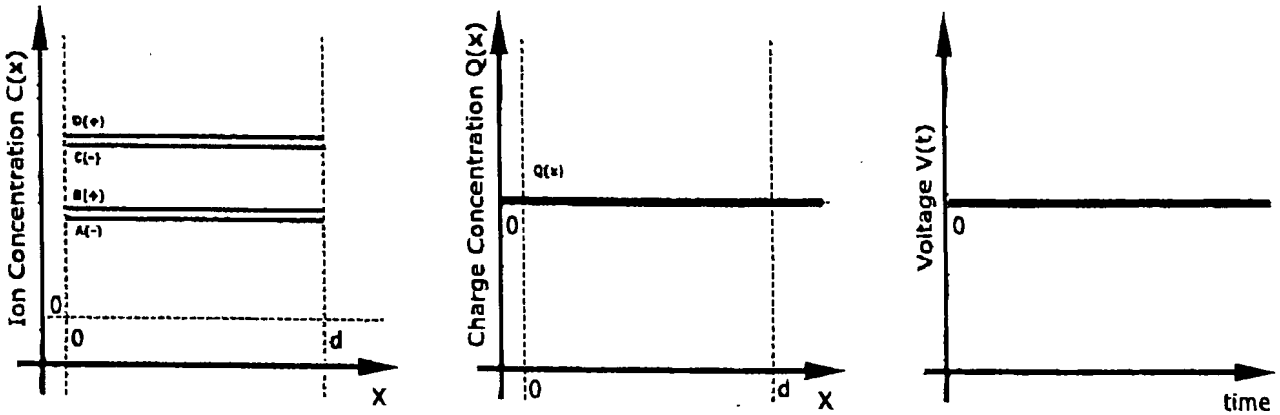


1.2) If A is spatially immobilized and B is free in the medium, the reaction causes a net transient gradient (current density) of B toward A. This transient current creates a temporary potential difference in the medium.

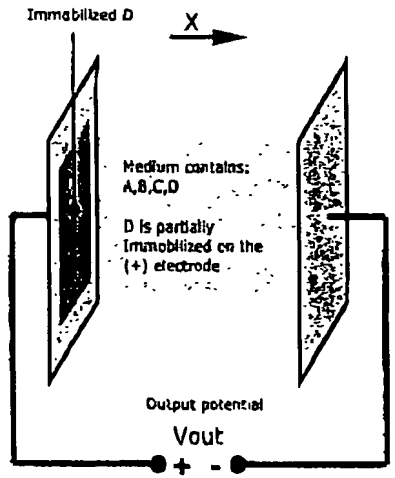
1.3 Potential difference between electrodes equilibrium (steady state):

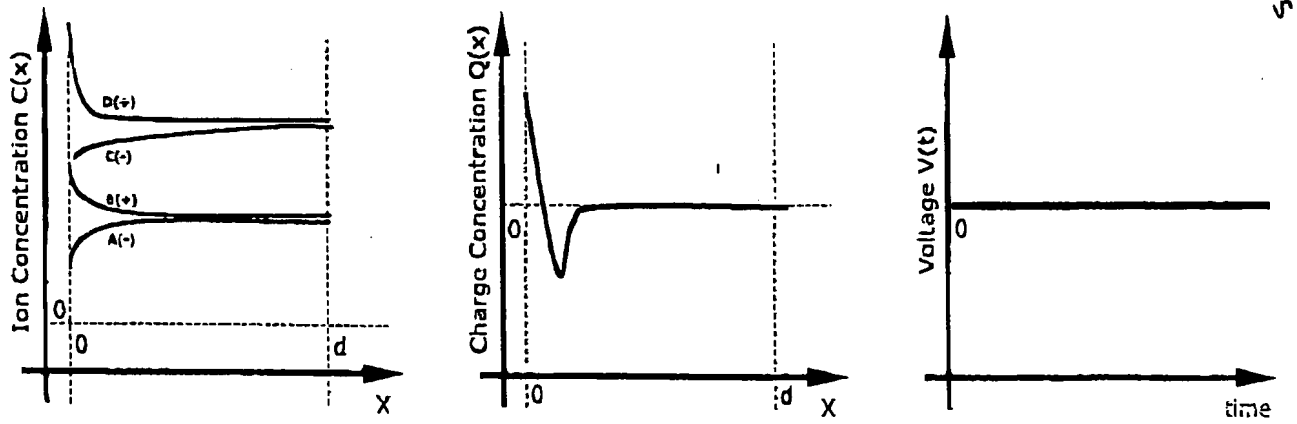
1) Electrodes are inert and do not interact with medium.
2) Four molecules (ions) A, B, C and D are present in the medium.
3) Molecules have arbitrary diffusion length and charge.





1.3.a) All molecules are free in the medium. Concentration of all molecules is uniform in equilibrium.

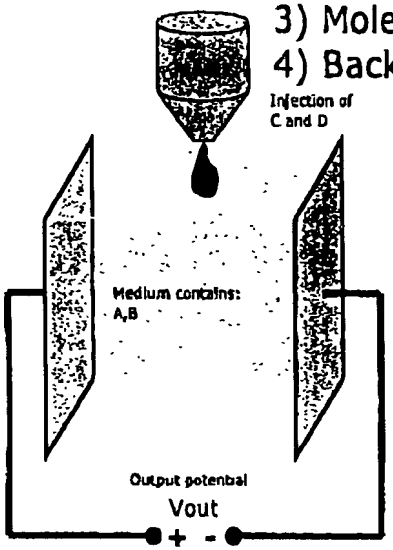


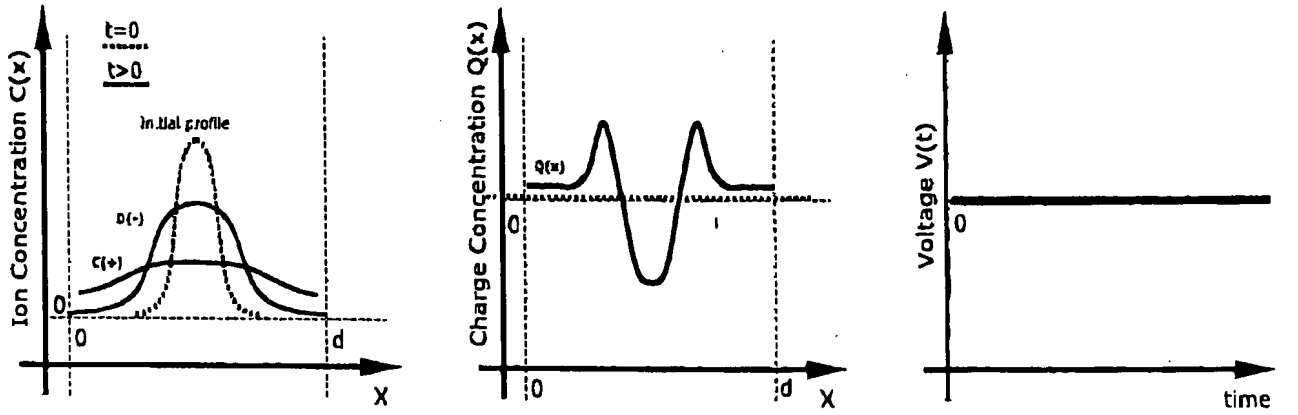


1.3.b) D is partially immobilized on the surface of the (+) Electrode which forces a none uniform concentration of molecules.

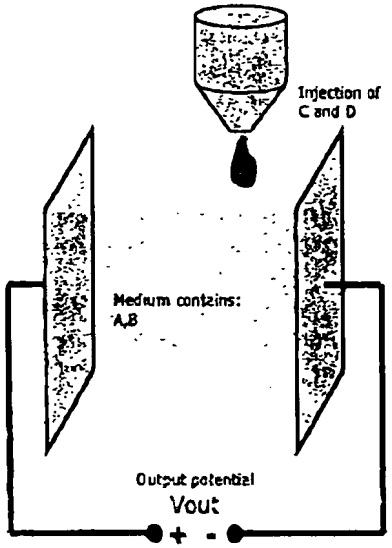
1.4 Potential difference between electrodes in none-equilibrium (transient) state:

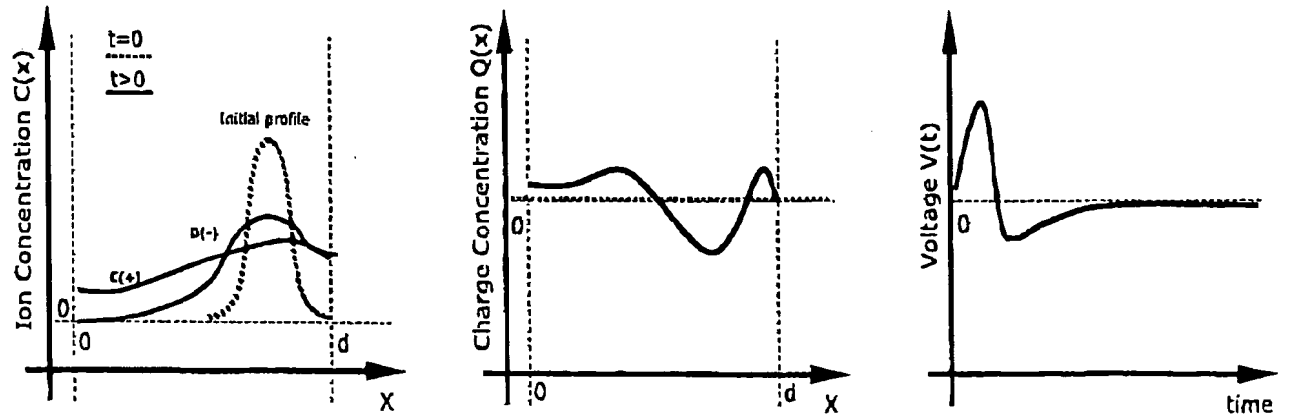
1) Electrodes are inert and do not interact with the medium.
2) Two molecules (ions) are present in the medium and two are added.
3) Molecules have arbitrary diffusion length and charge.
4) Background molecules are not shown (A and B).





1.4.a) C and D are added symmetric to the electrodes.

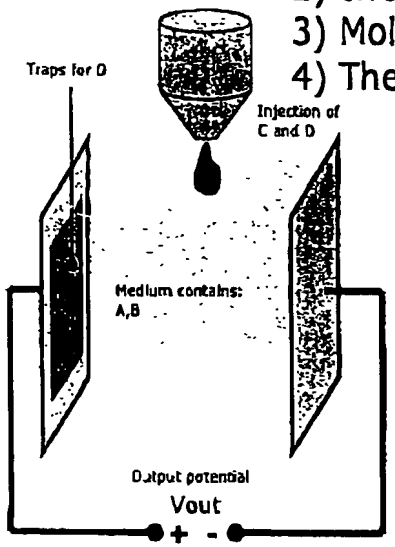


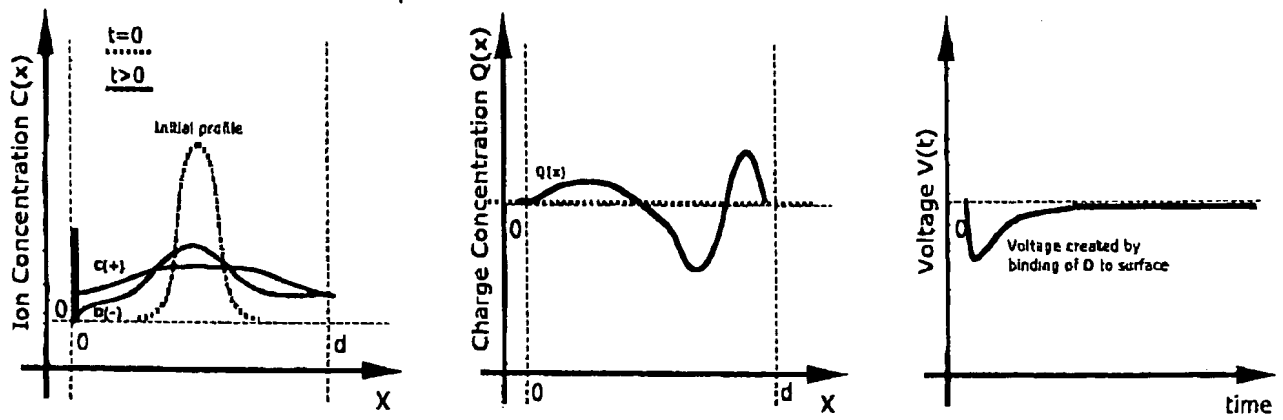


1.4.b) C and D are added asymmetric to the electrodes and an ionic perturbation is generated.

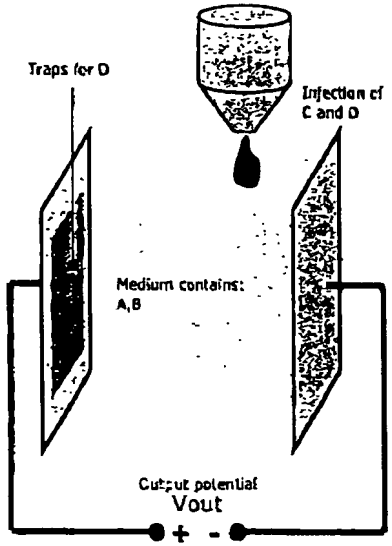
1.5 Potential difference between electrodes in the none-equilibrium (transient) with surface trap:

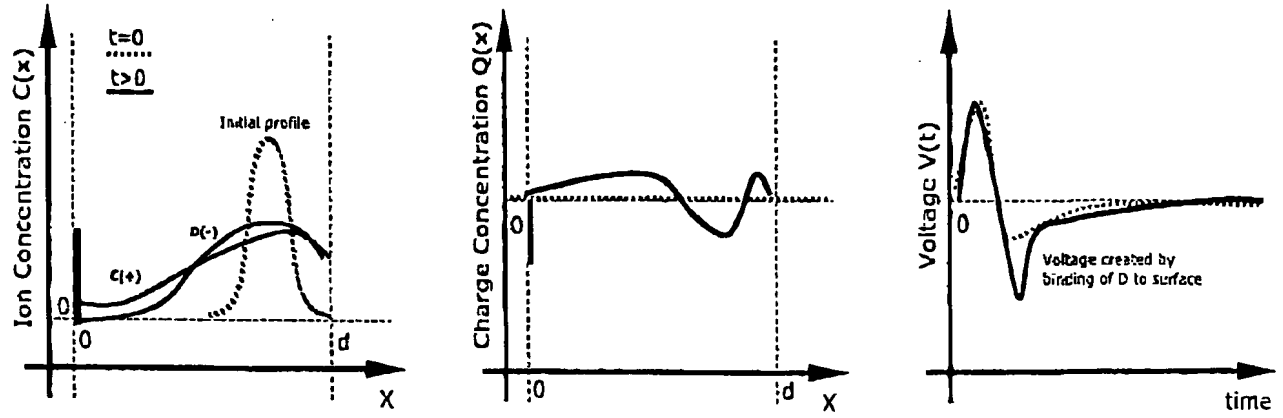
1) Electrodes are inert and do not interact with the medium.
2) two molecules (ions) are present in the medium and two are added in time.
3) Molecules have arbitrary diffusion length and charge.
4) The (+) electrode has finite traps for D on the surface.





1.5.a) C and D are added symmetric to the electrodes. Traps cause a potential perturbation.

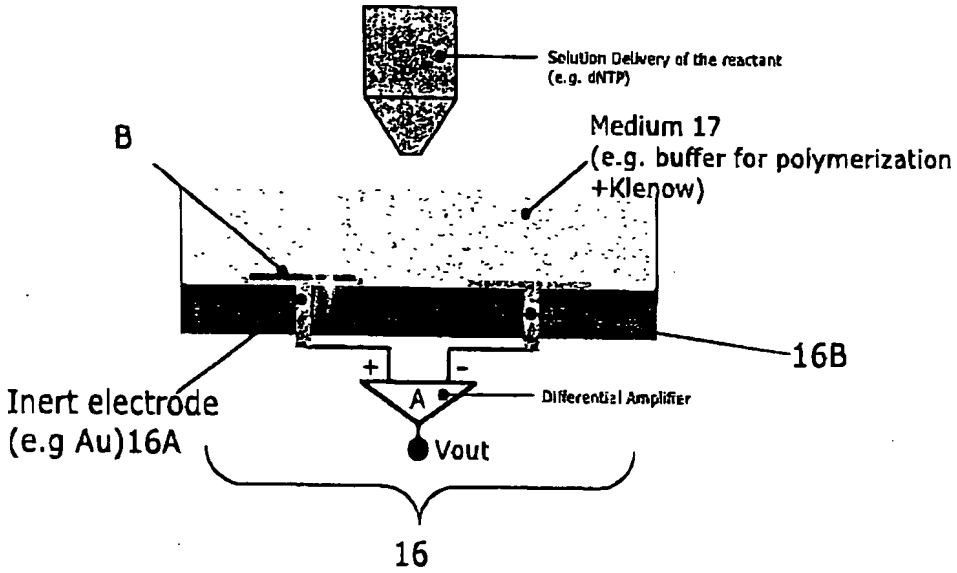




1.5.b) C and D are added asymmetric to the electrodes, and an extra electric field perturbation is created by the traps.

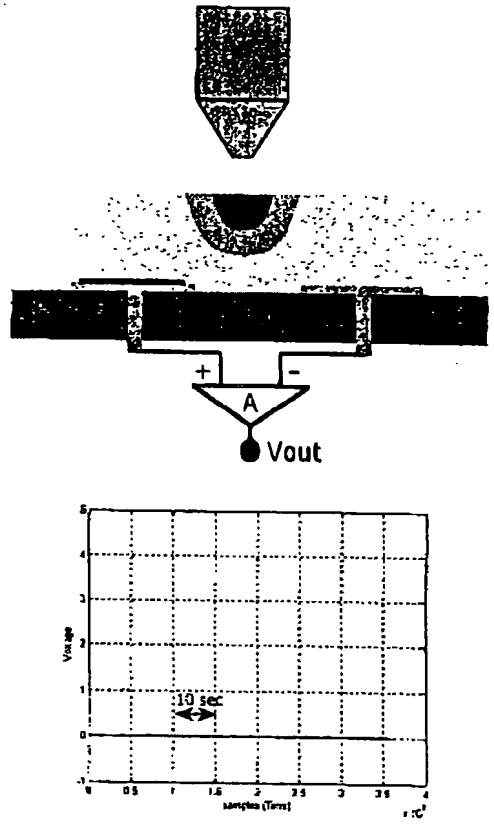
2.1 Planar sensor design example:

1) Electrodes are inert and do not interact with the medium.
2) The target molecules are immobilized on the (+) electrode.
3) The (-) electrode is the reference electrode.
4) A differential amplifier subtracts the voltage from the two electrodes.

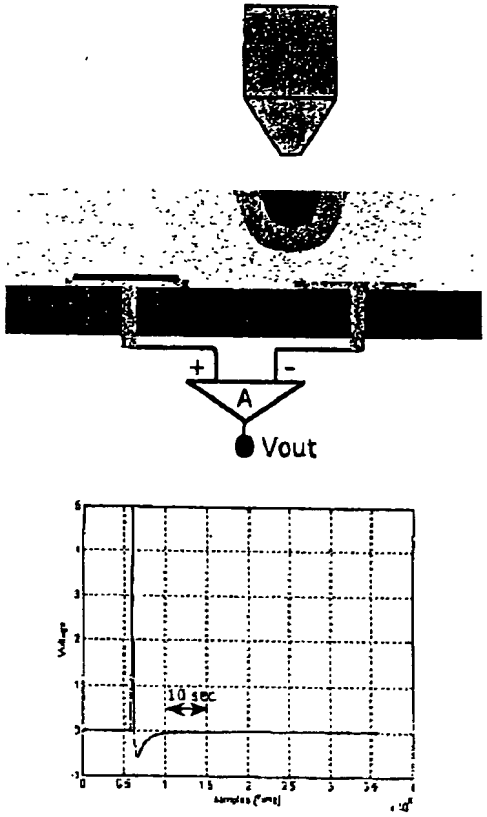


2.2 Example of signal generated when no binding at the surface occurs :

1) Electrodes are inert and do not interact with the medium.
2) The target molecules are immobilized on the (+) electrode.
3) The (-) electrode is the reference electrode.
4) A differential amplifier subtracts the voltage of the two electrodes.



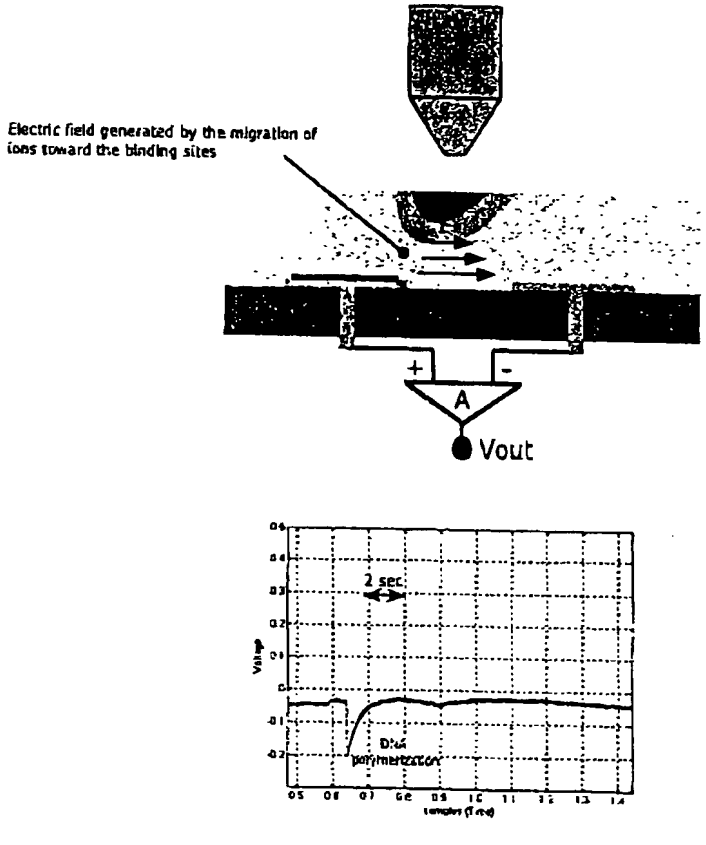
a) Solution is delivered symmetric to the electrodes
With 0.1 pmol immobilized ssDNA.



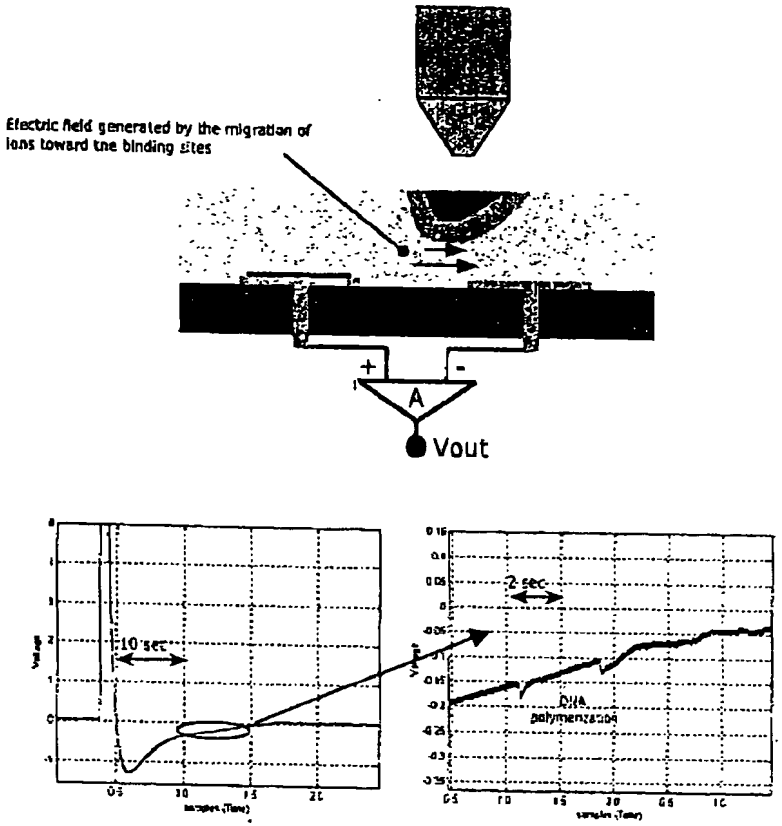
b) Solution is delivered asymmetric to the electrodes
With 0.1 pmol immobilized ssDNA.

2.3 Example of signal generated when binding at the surface occurs:

1) Electrodes are inert and do not interact with the medium.
2) The target molecules are immobilized on the (+) electrode.
3) The (-) electrode is the reference electrode.
4) A differential amplifier subtracts the voltage from the two electrodes.

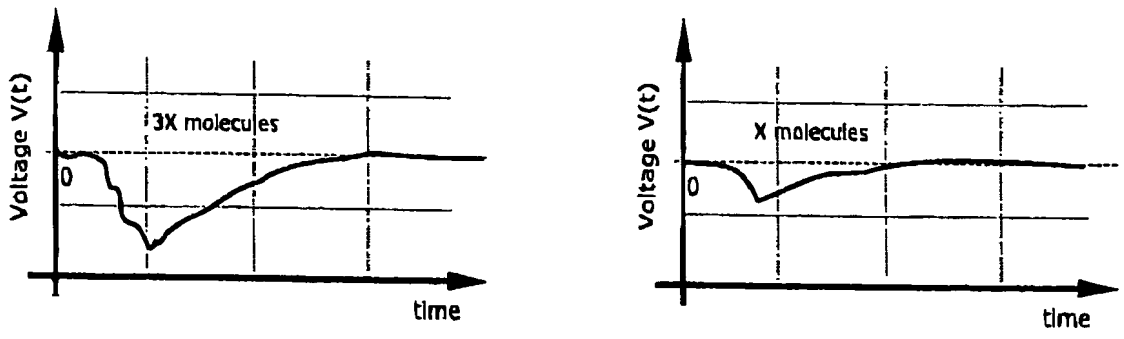


a) Solution is delivered symmetric to the electrodes, Polymerization of 0.1 pmol primed ssDNA.

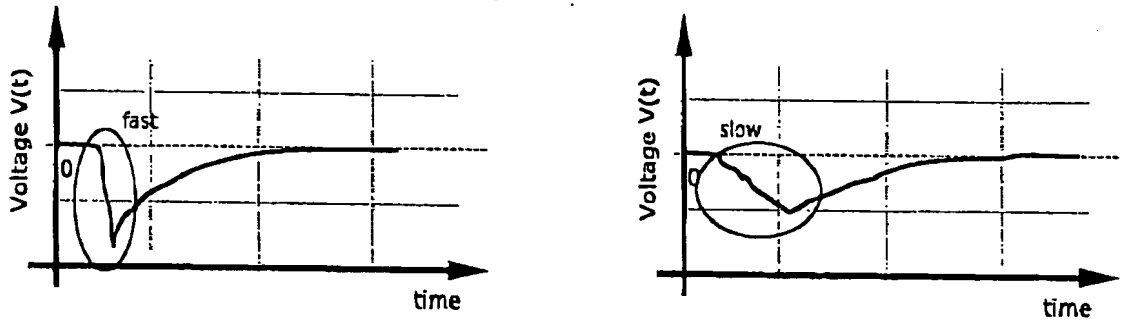


b) Solution is delivered asymmetric to the electrodes Polymerization of 0.1 pmol primed ssDNA.

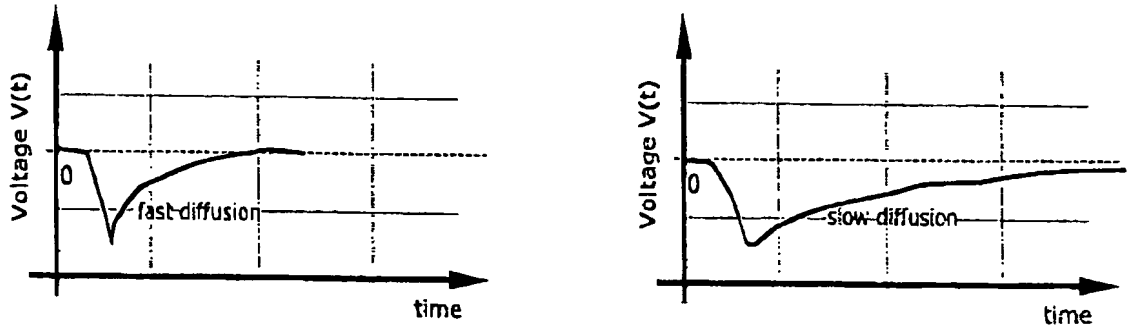
2.4 Analysis examples of the transient signal generated:



a) Quantity of molecules

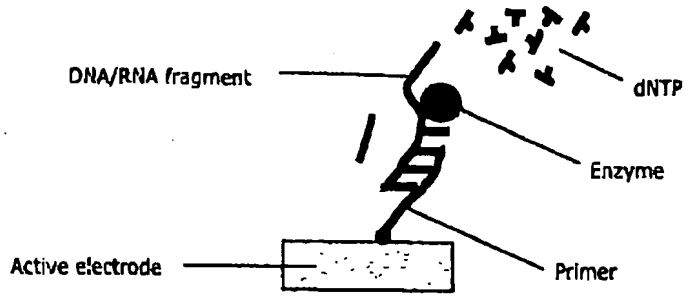


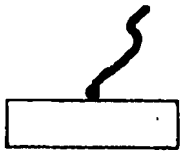
b) Kinetics (speed) of the reaction



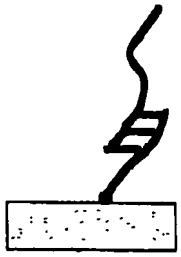
a) Movement and diffusion of molecules.

FIGURE 3:
Sequencing

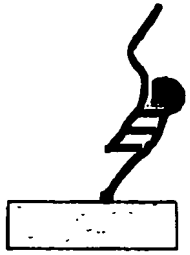




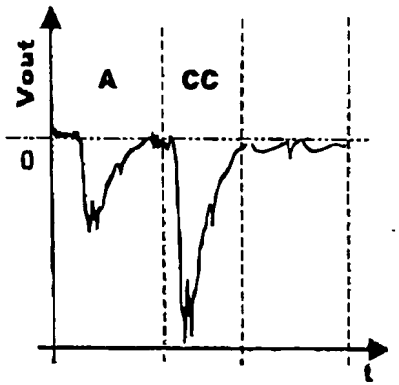
Gene specific primer

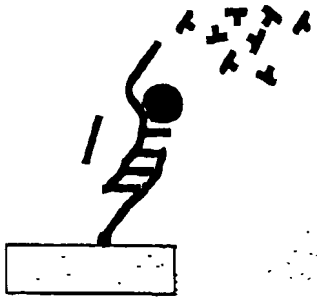


Hybridization of DNA/RNA to primer

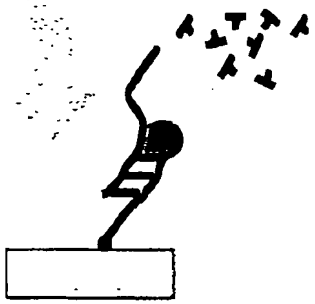


Addition of Enzyme





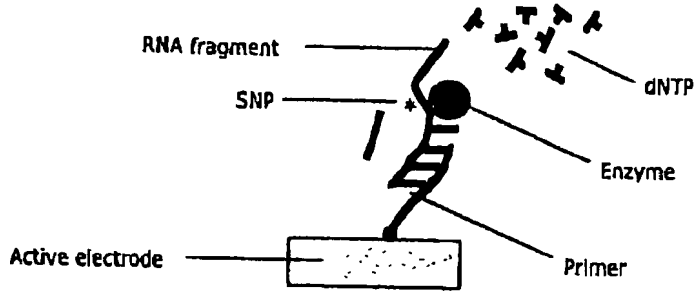
Right nucleotide added and signal generation

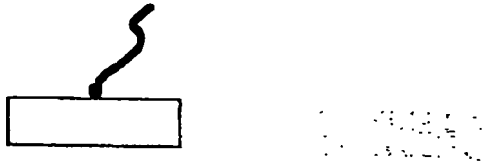


Addition of specific Nucleotide one at a time or all at the same time

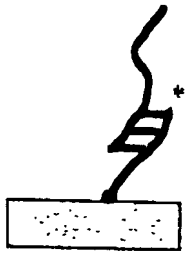
FIGURE 4:1

SNP detection by using Total RNA

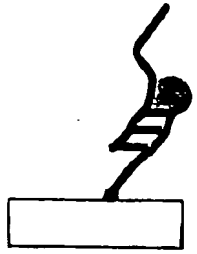




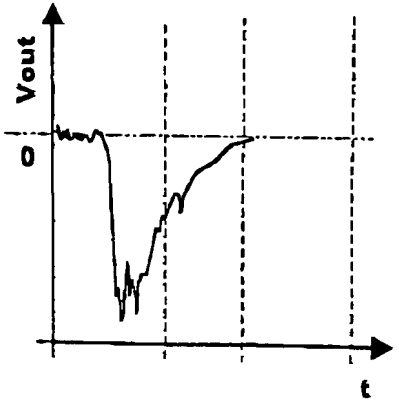
Gene specific designed primer around the SNP

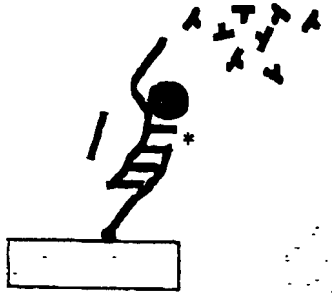


Hybridization of RNA to Specific primer

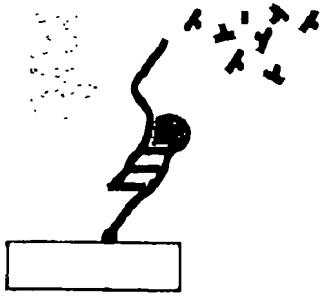


Addition of Enzyme





Correct nucleotide generates signal



Addition of specific nucleotide

FIGURE 4:2

SNP detection by using cDNA

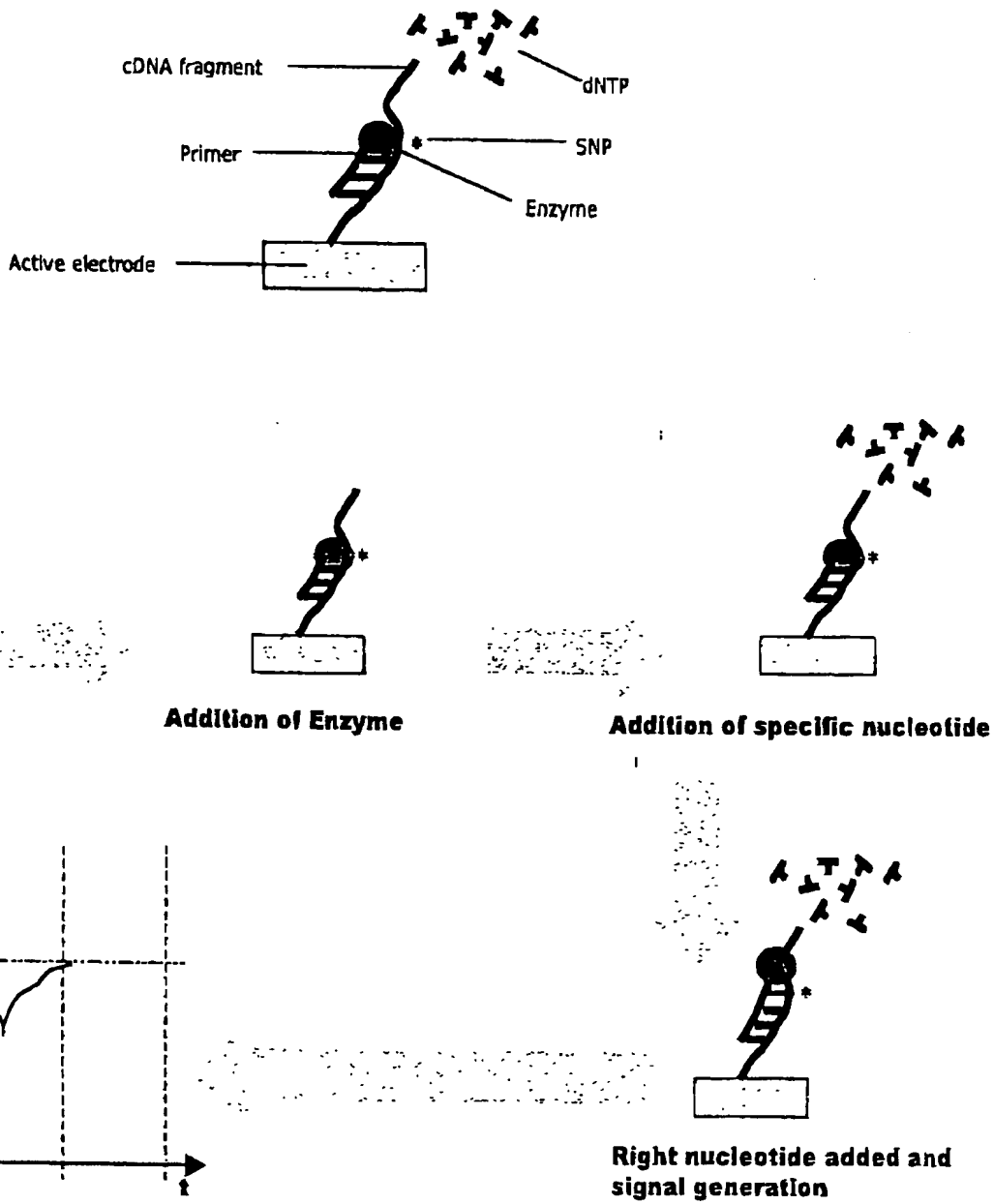
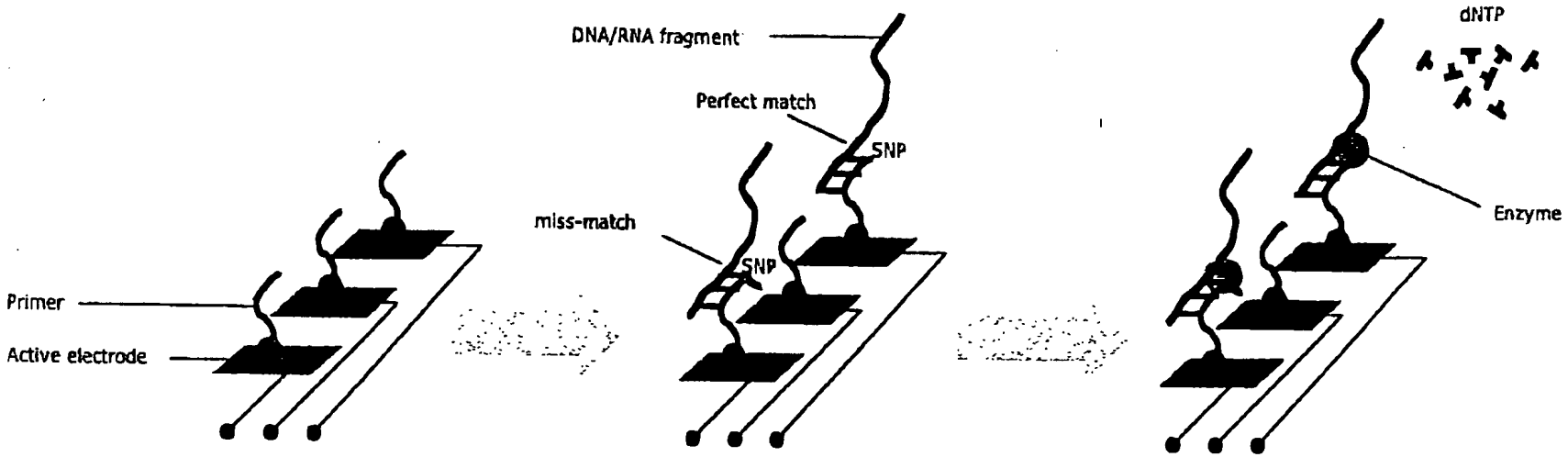


FIGURE 4:3

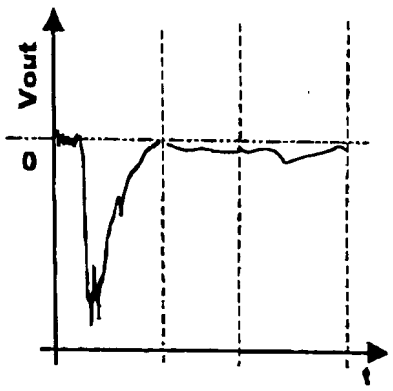
SNP detection by using allele specific primer

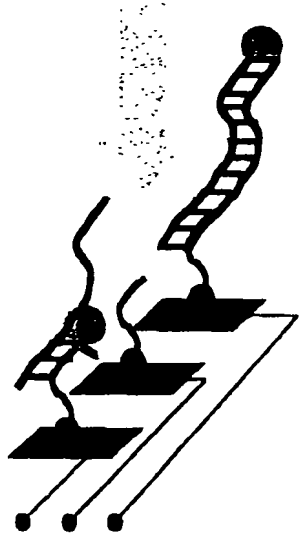


Allele specific primers

Hybridization of DNA/RNA to primer

Addition of Enzyme & dNTP

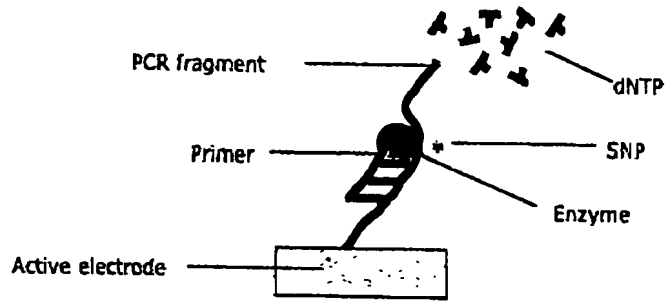


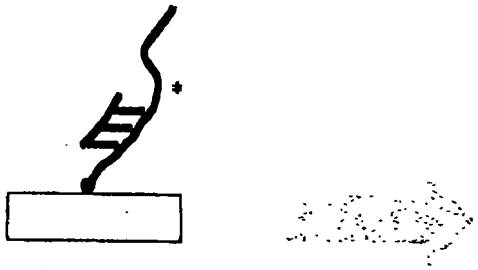


Perfect match primer/template polymerizes and signal is generated

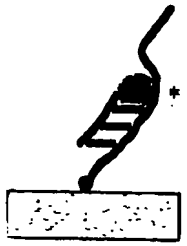
FIGURE 5:

SNP detection by using PCR product

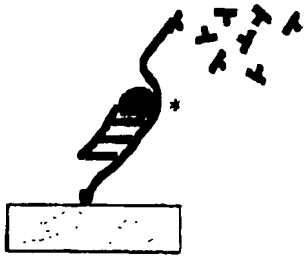




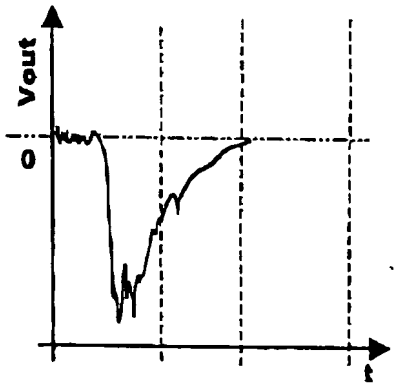
Annealing the specific designed primer around the SNP

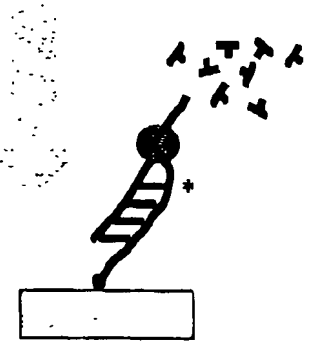


Addition of Enzyme



Addition of specific nucleotide





Right nucleotide added and signal generation

FIGURE 6:

SNP detection by using Exonuclease/ Degrading enzyme

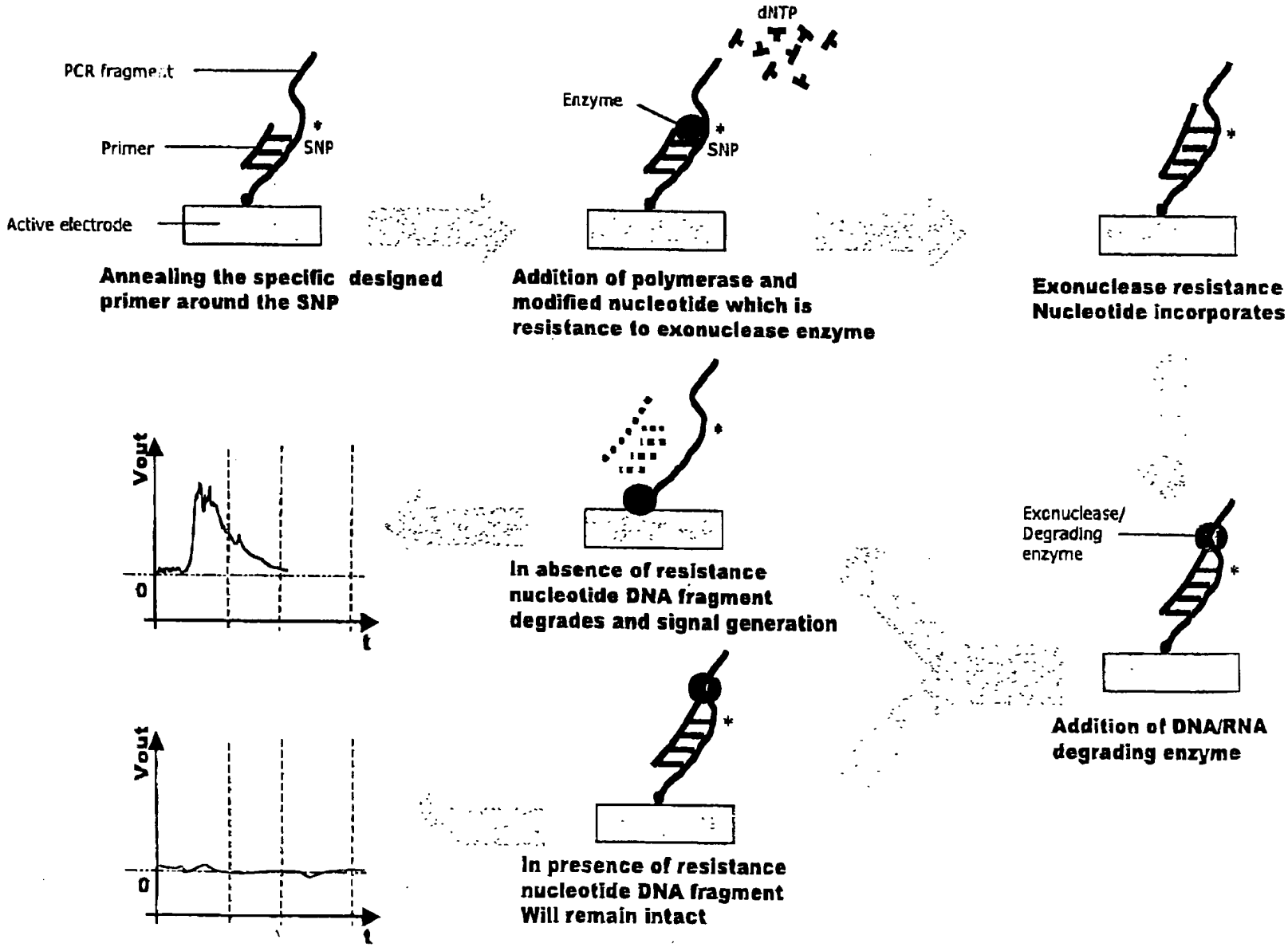


FIGURE 7:
Real time PCR

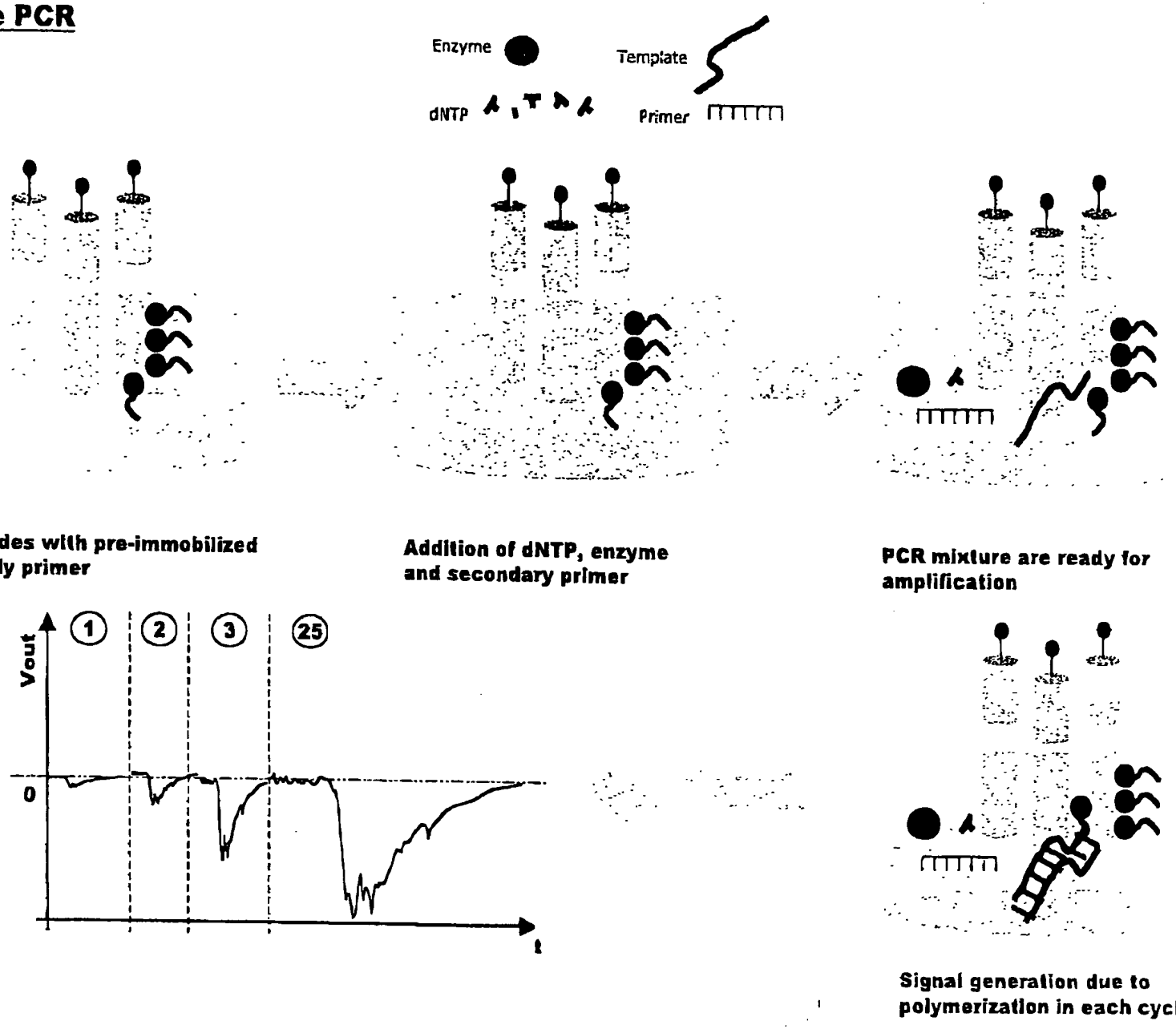
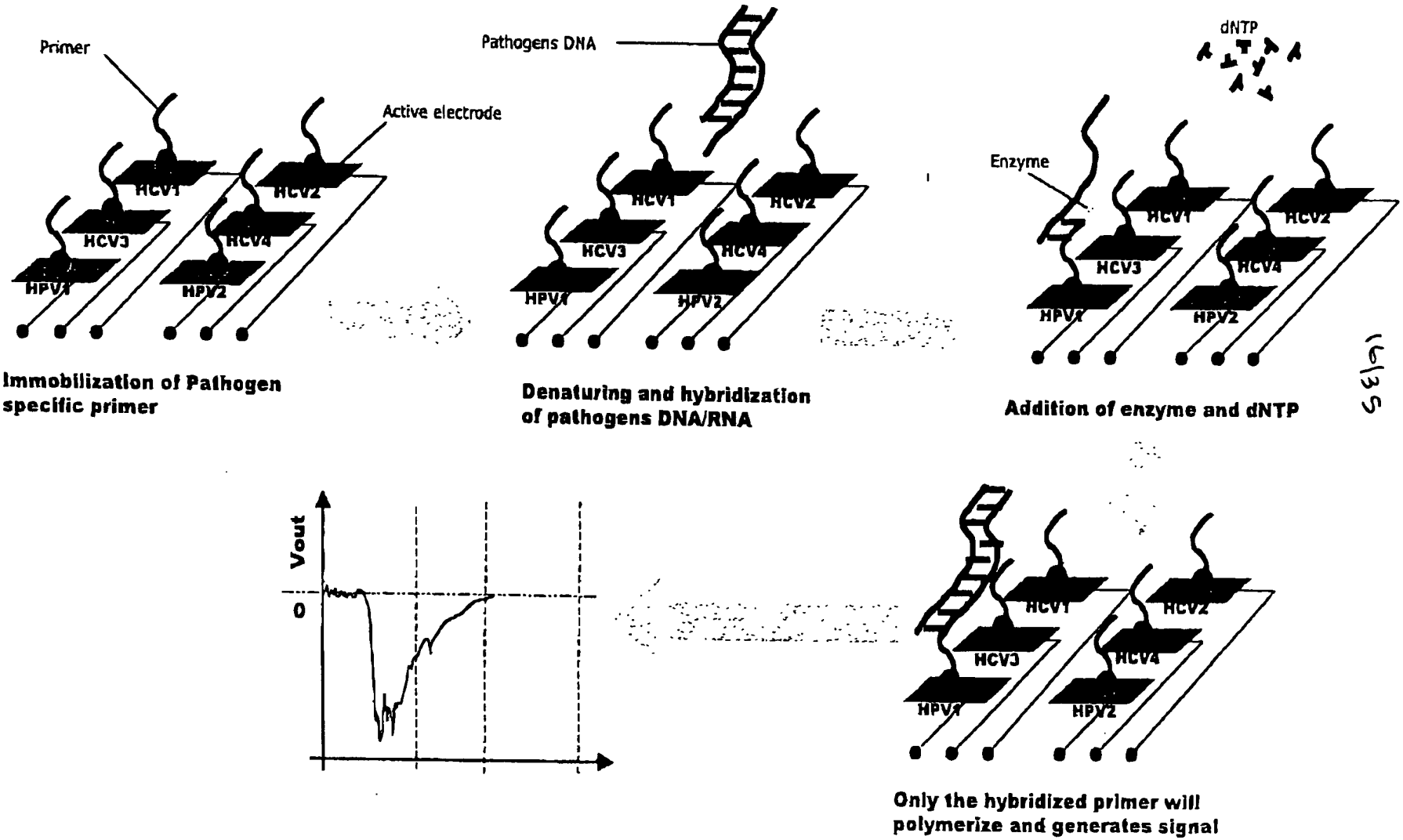


FIGURE 8:
Pathogen typing



Immobilization of Pathogen specific primer

Denaturing and hybridization of pathogens DNA/RNA

Addition of enzyme and dNTP

Only the hybridized primer will polymerize and generates signal

FIGURE 9:
Antigen-antibody detection

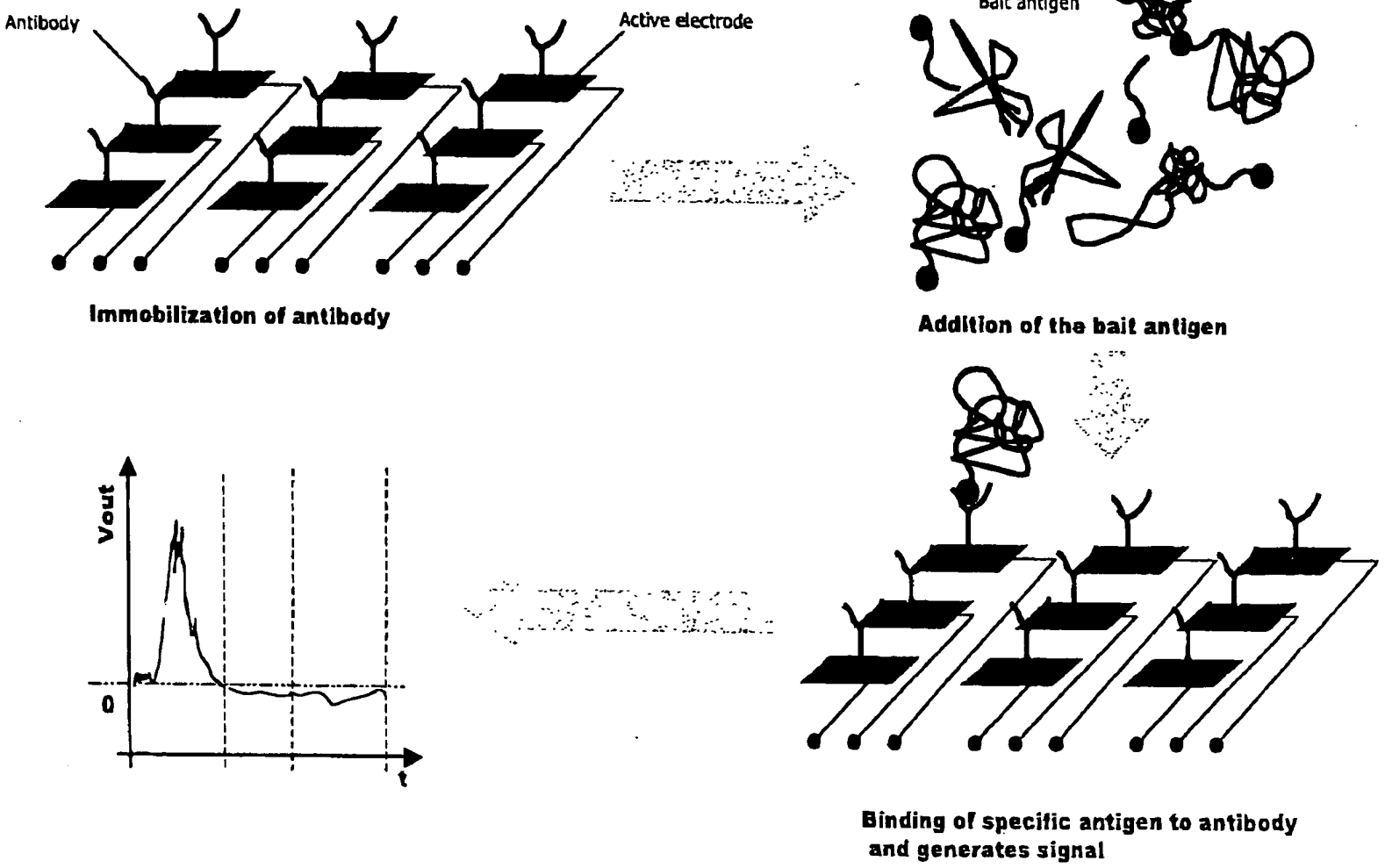
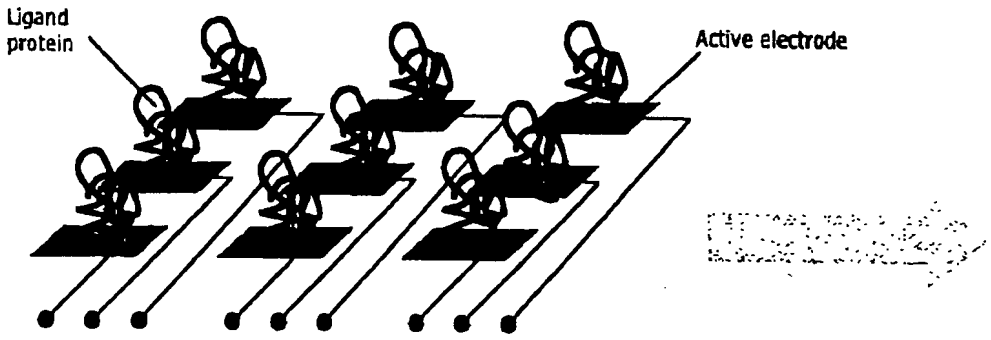
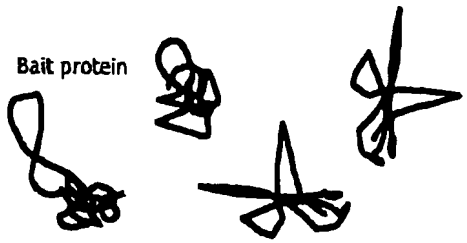


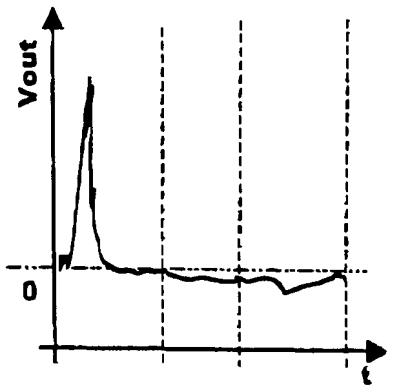
FIGURE 10:
Protein-protein interaction

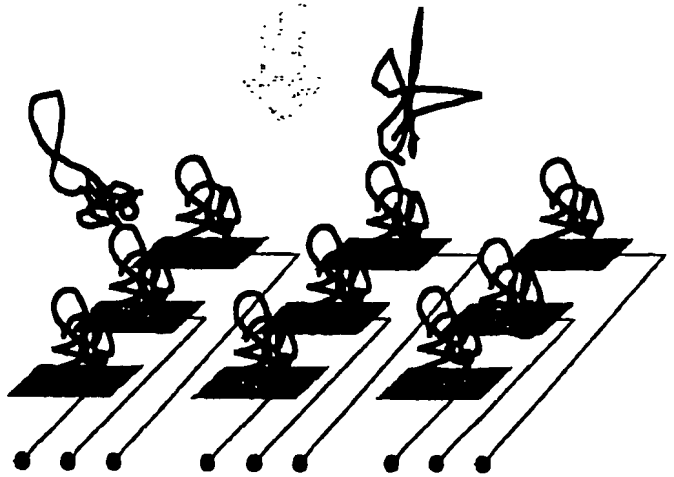


Immobilization of different ligand protein



Addition of the bait proteins





Specific protein-protein interaction and generates signal

FIGURE 11:
Ligand and receptor detection

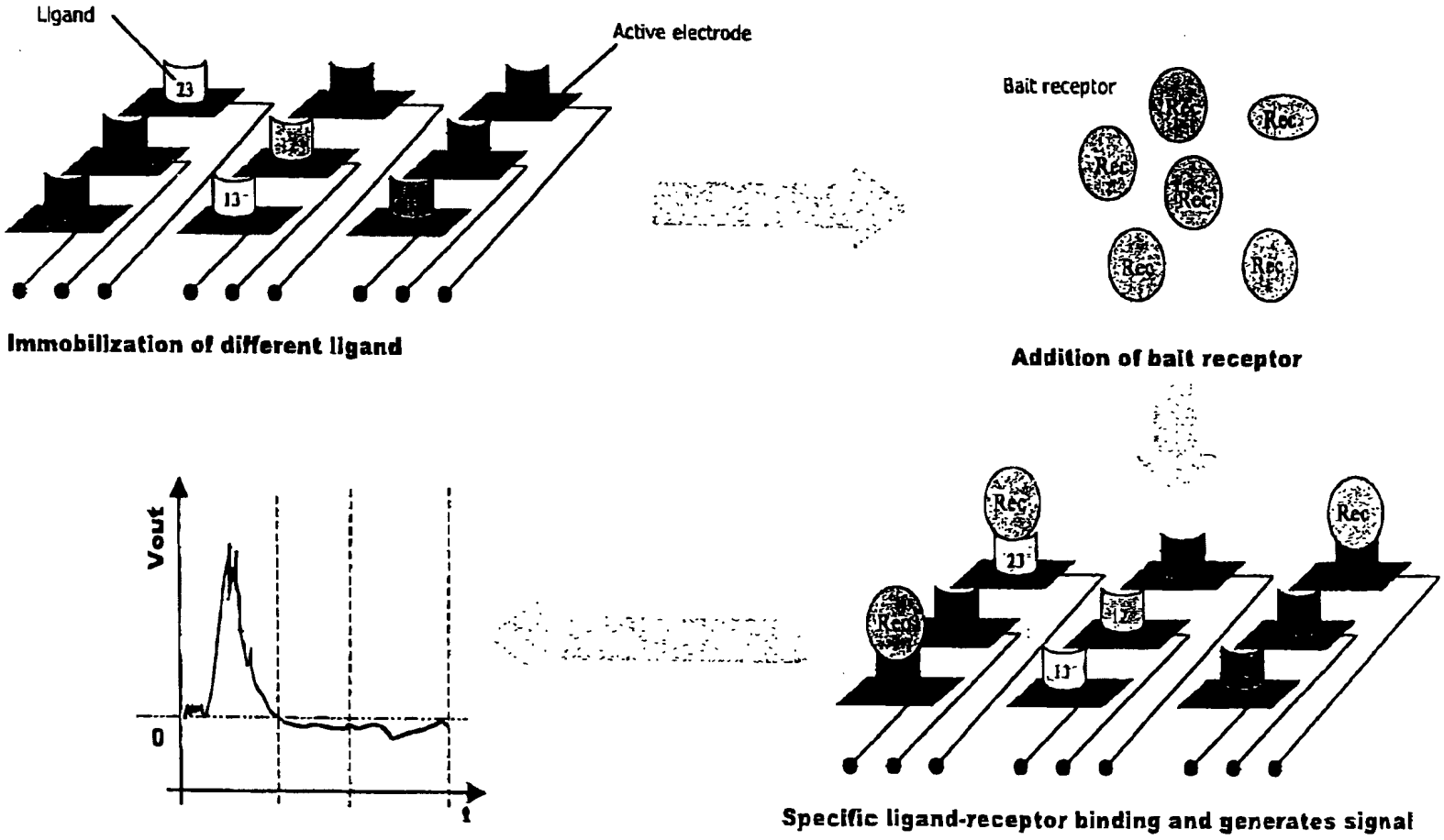
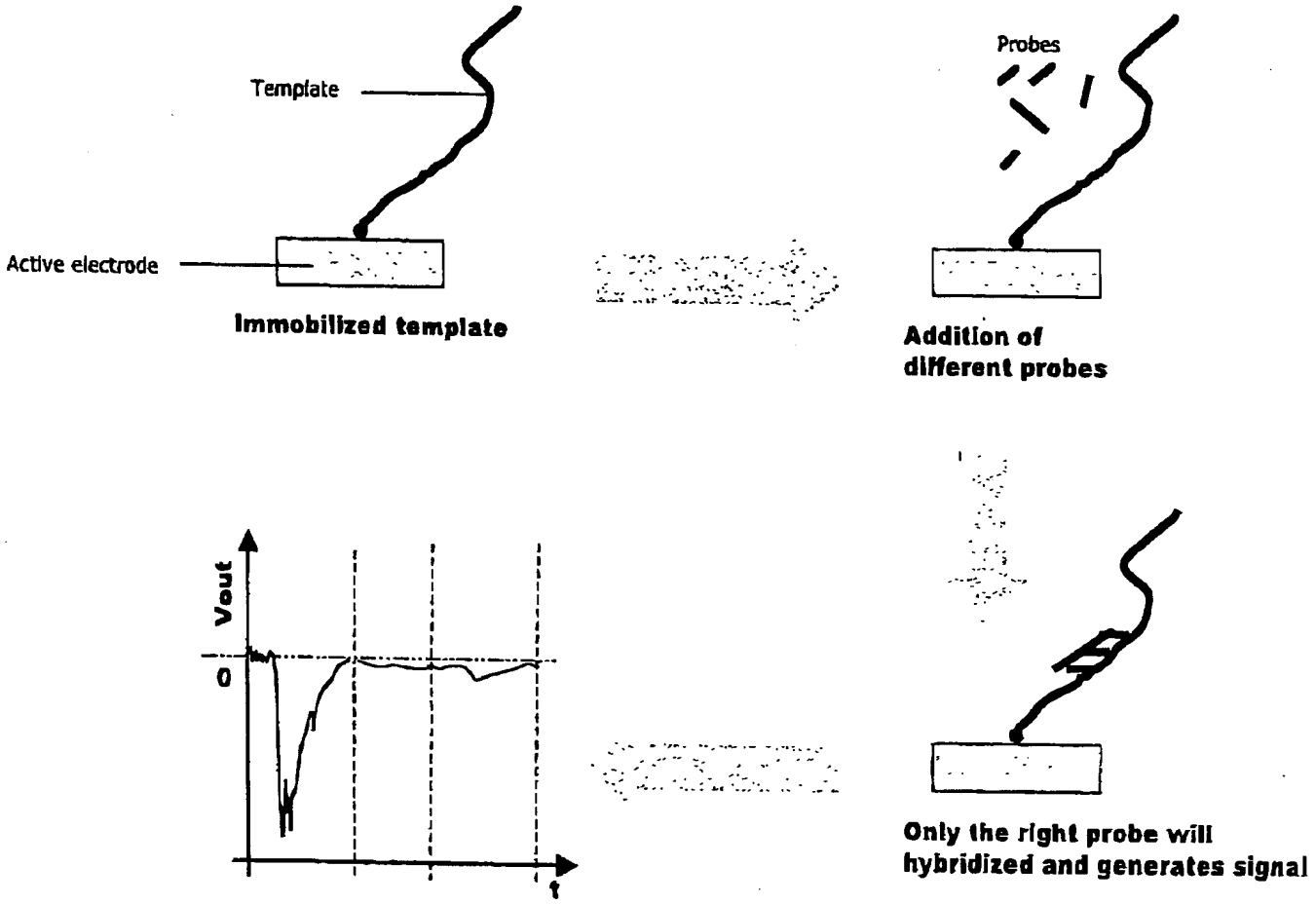


FIGURE 12:
Hybridization



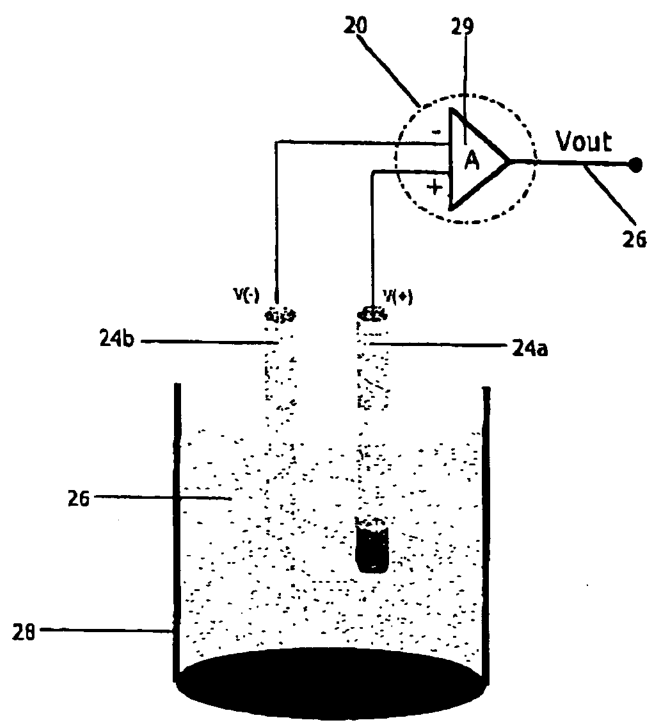


Fig: 13

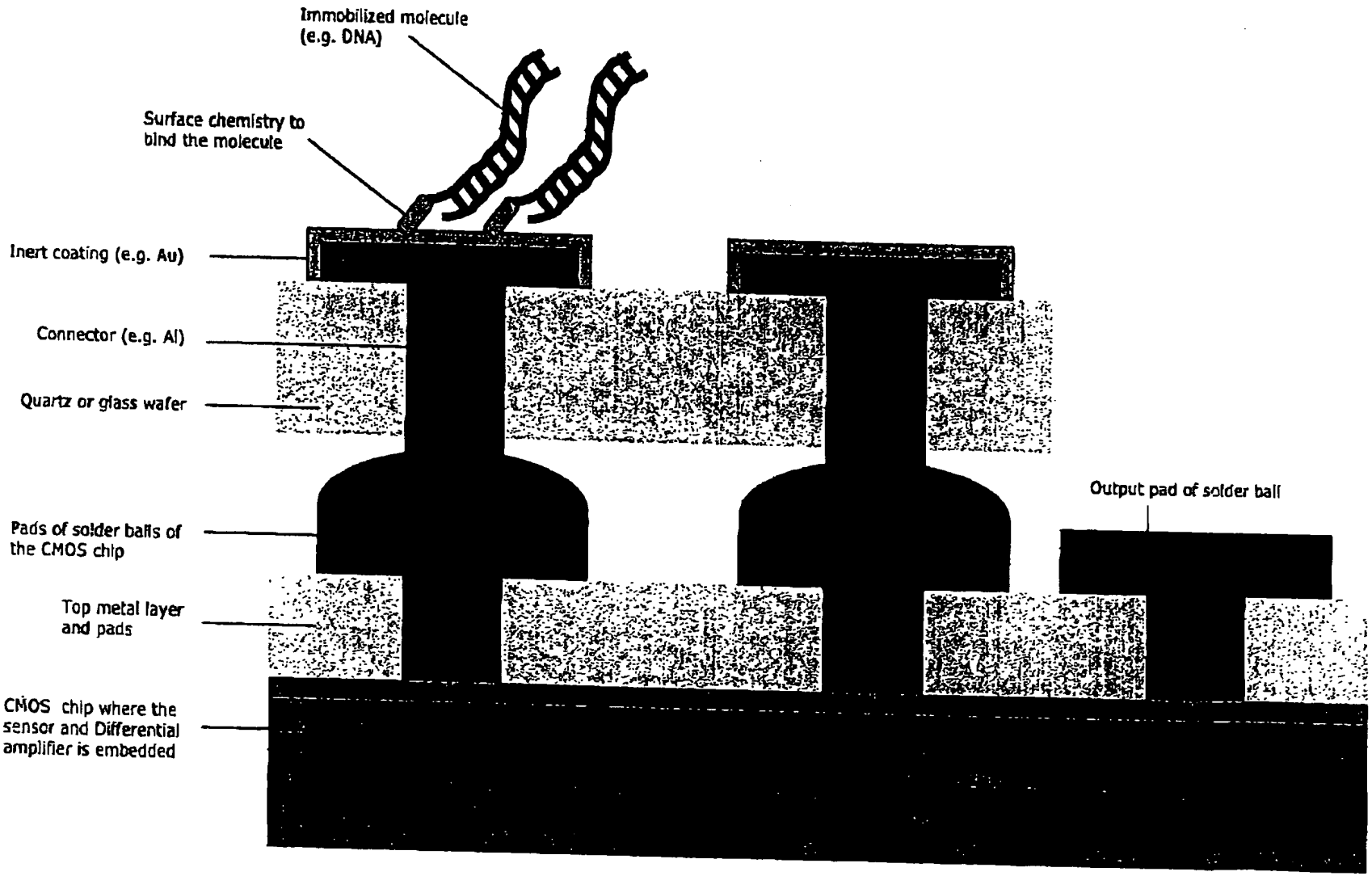

Immobilized molecule
(e.g. DNA)
Surface chemistry to
bind the molecule
Inert coating (e.g. Au)
Connector (e.g. Al)
Quartz or glass wafer
Pads of solder balls of
the CMOS chip
Top metal layer
and pads
CMOS chip where the
sensor and Differential
amplifier is embedded
Output pad of solder ball

Fig: 14

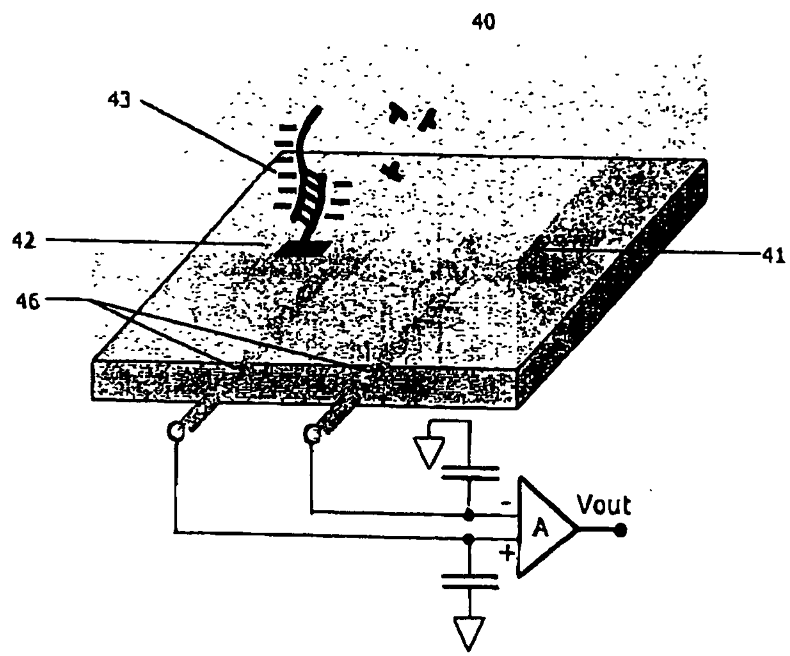


Fig: 15

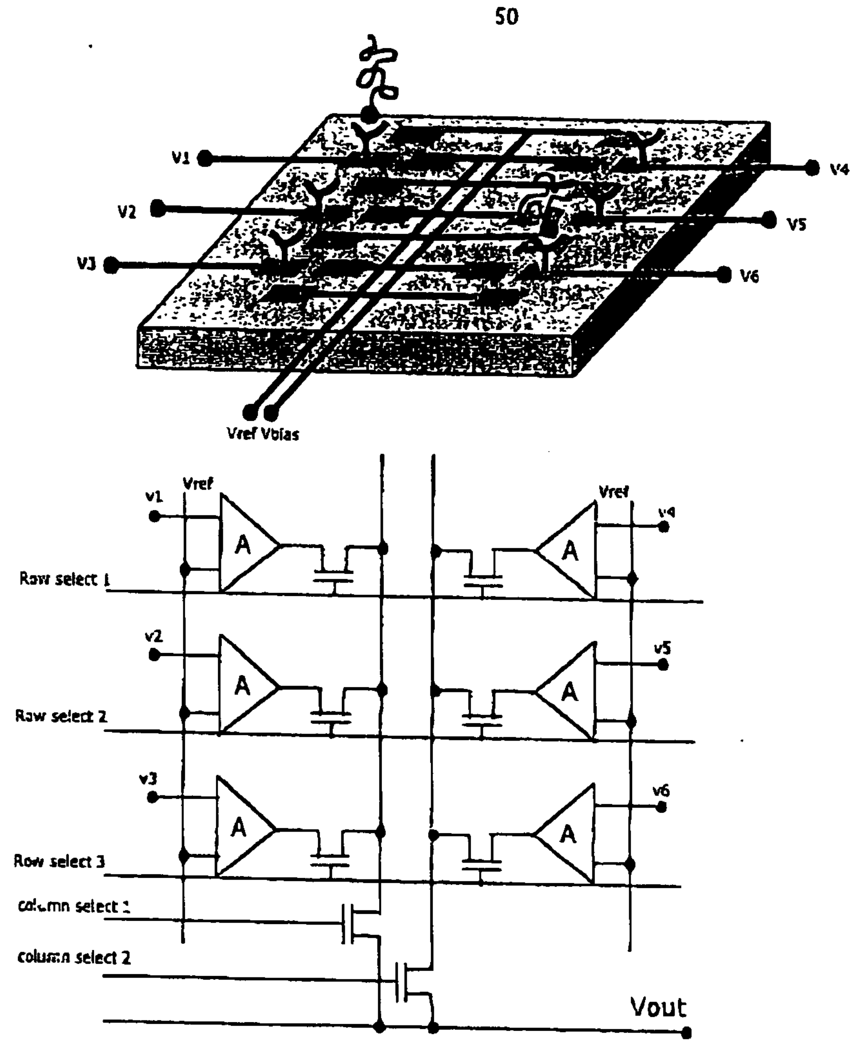
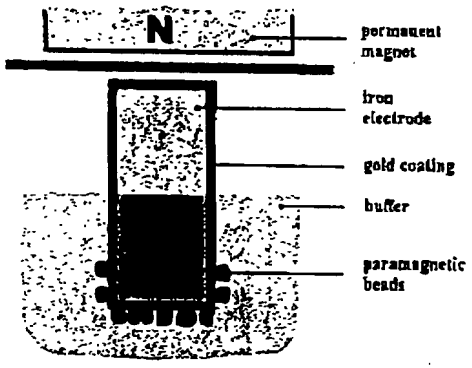


Fig: 16

Figure 17A: PCR product attracts to an electrode by using a permanent magnet and paramagnetic beads.



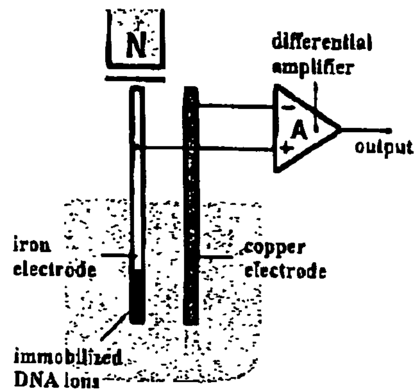


Figure 17 B: Basic model of the sensor with a differential amplifier

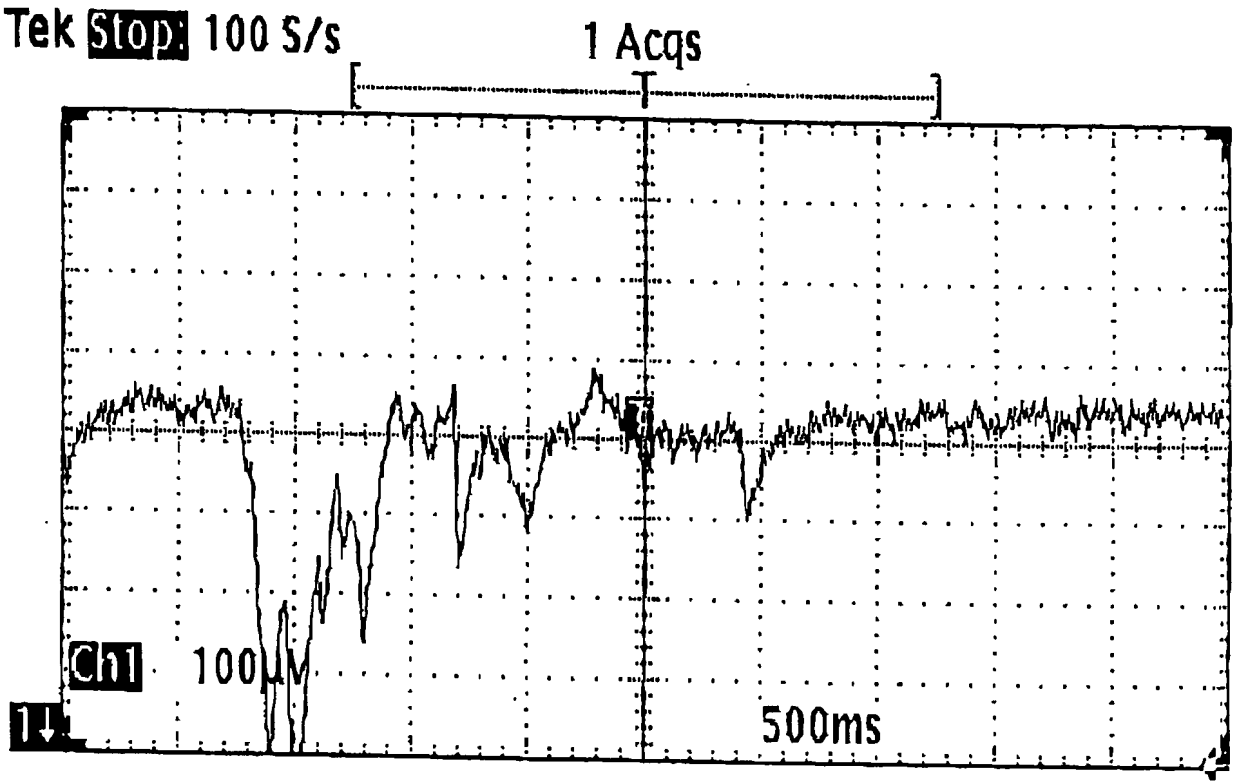


Figure 18 A: some sample charge sequencing extension signatures for 300 bp DNA

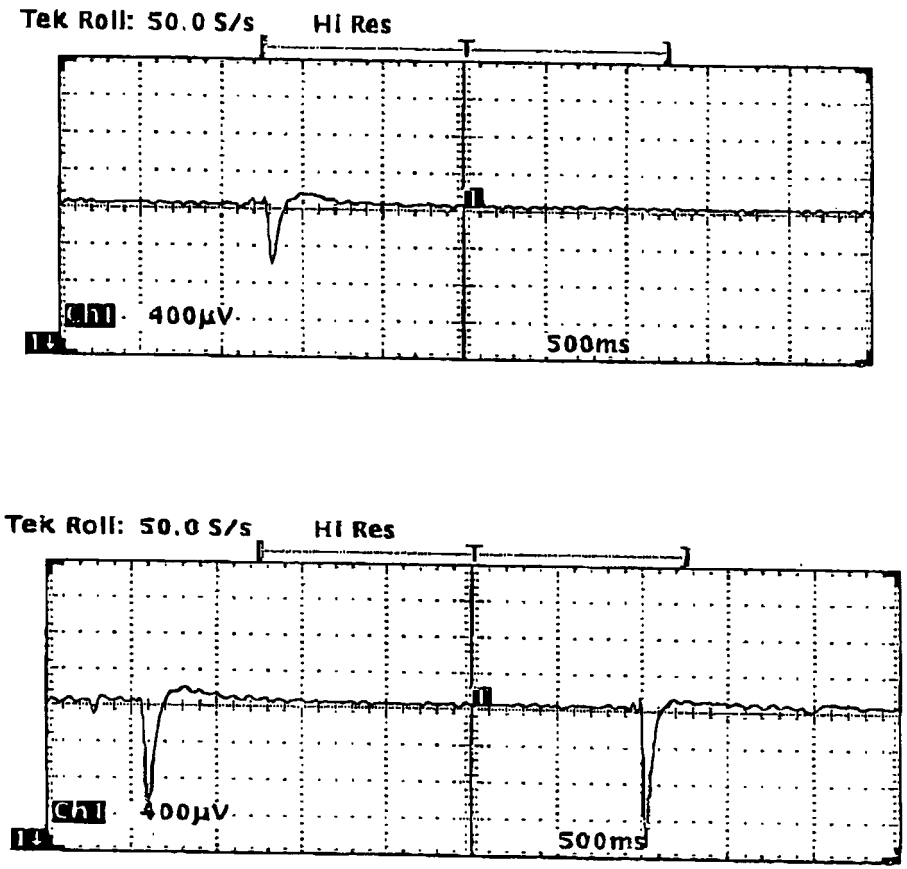


Figure 18 B: More sample charge sequencing extension signatures for 300 bp DNA with two different concentration of Immobilized DNA (0.05 pmol and 0.1 pmol)

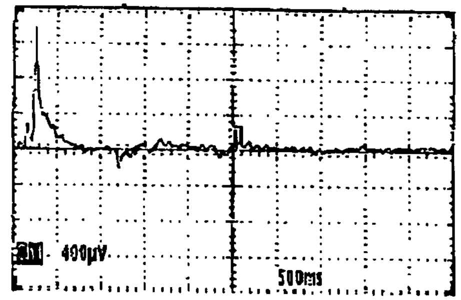


Figure 18C.

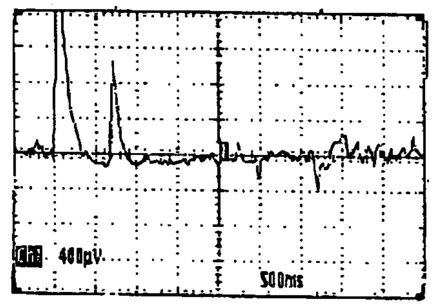


Figure 18D.

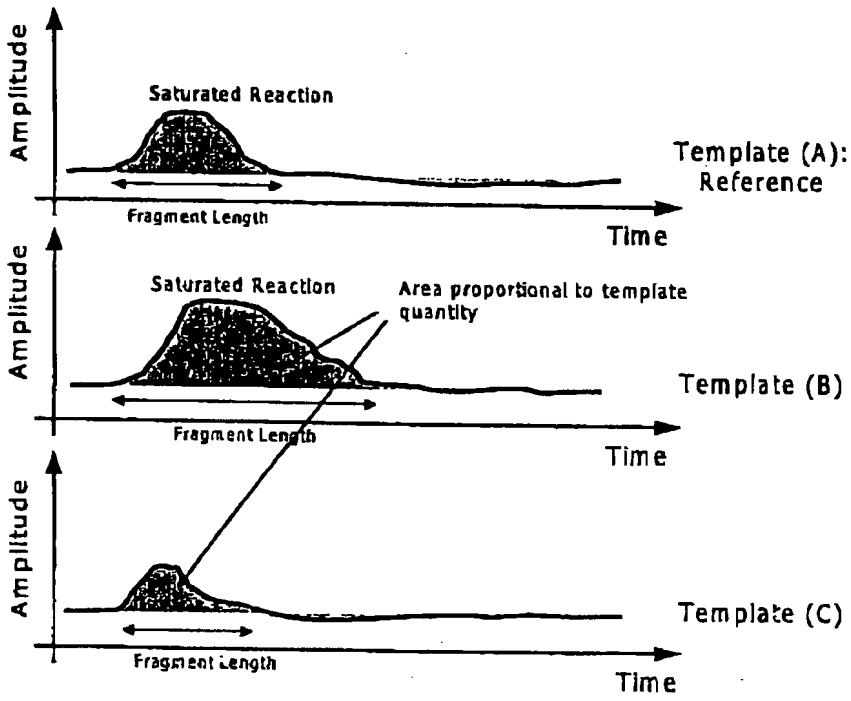
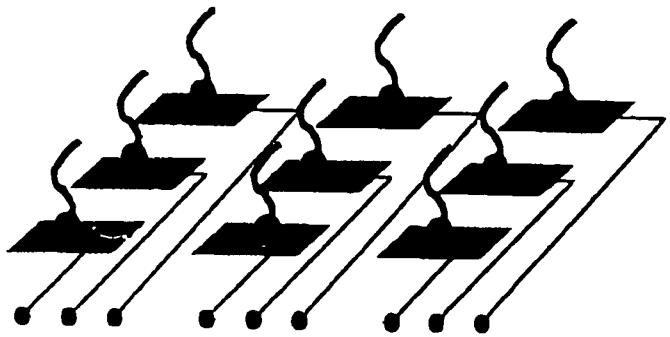


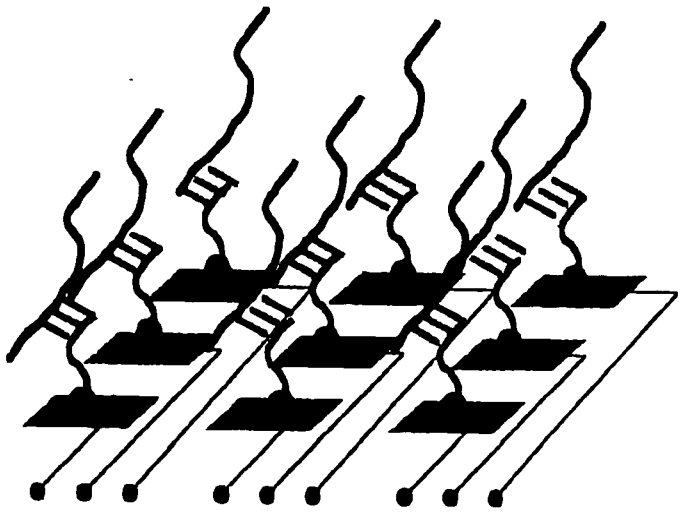
FIGURE 18E

FIGURE 19 a:

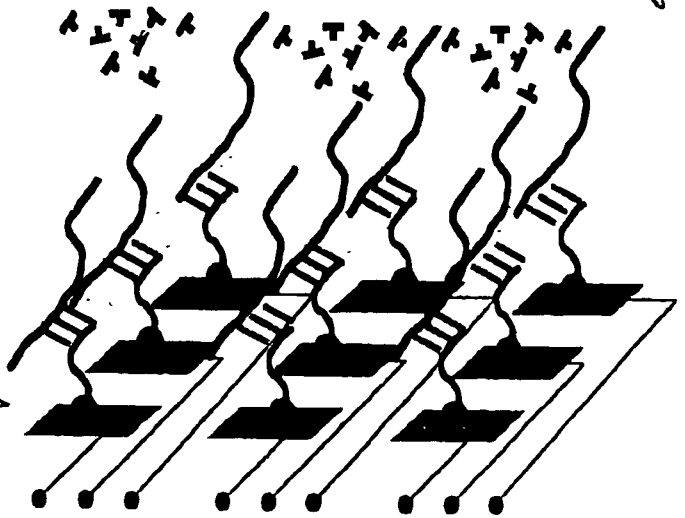
Gene Expression profiling by using Total RNA



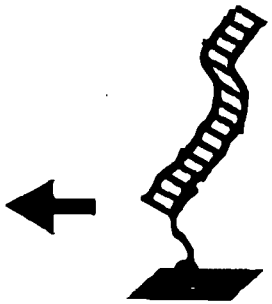
Gene specific designed primer



Hybridization of RNA to Specific primer



Addition of enzyme and nucleotide



Right nucleotide added and Generates signal

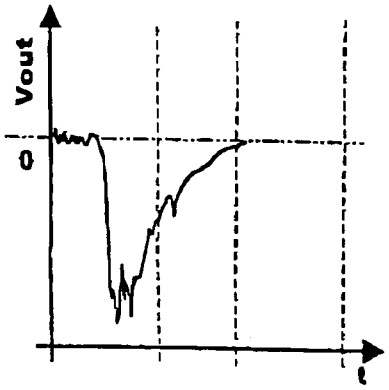
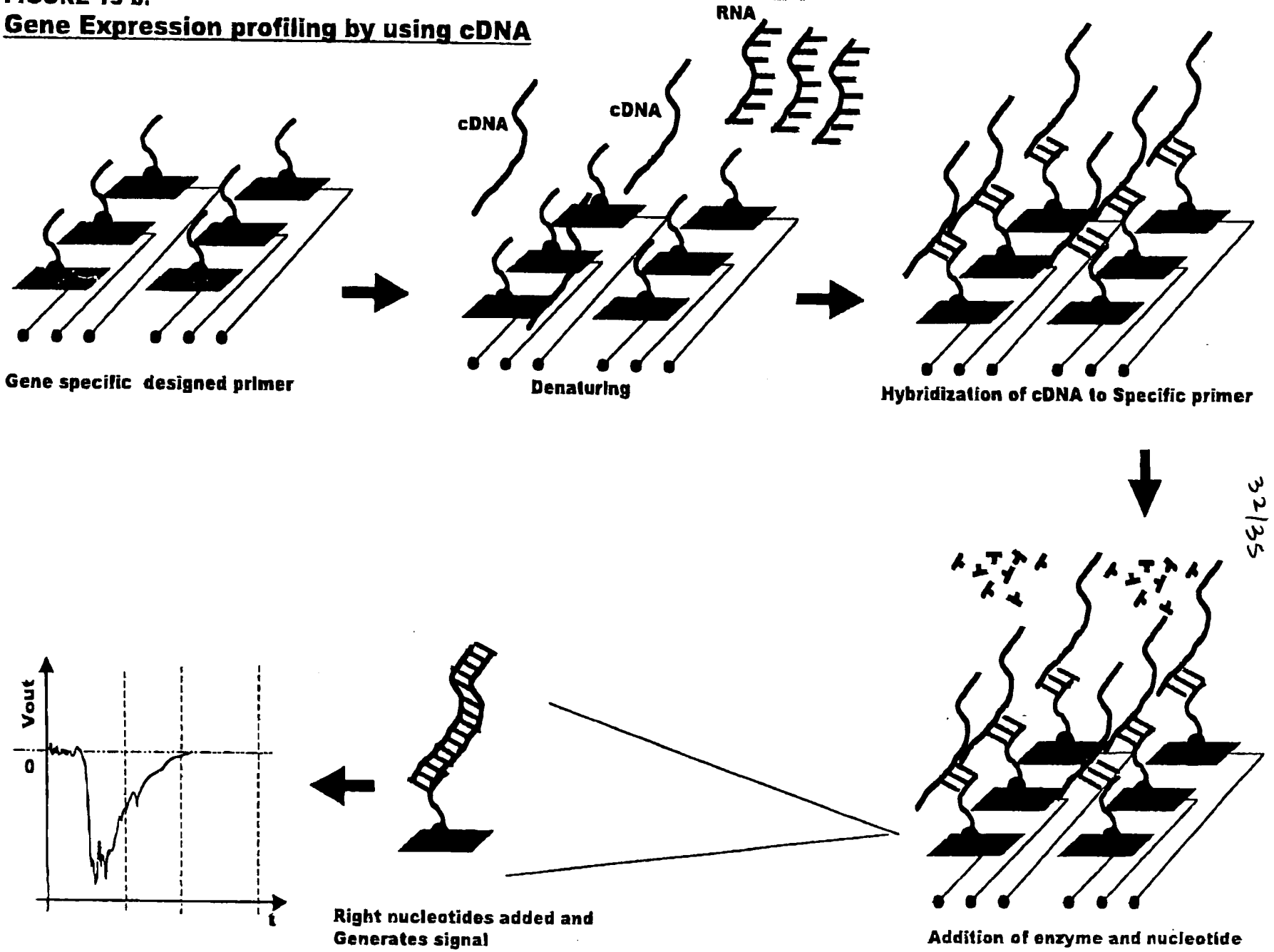


FIGURE 19 b:

Gene Expression profiling by using cDNA



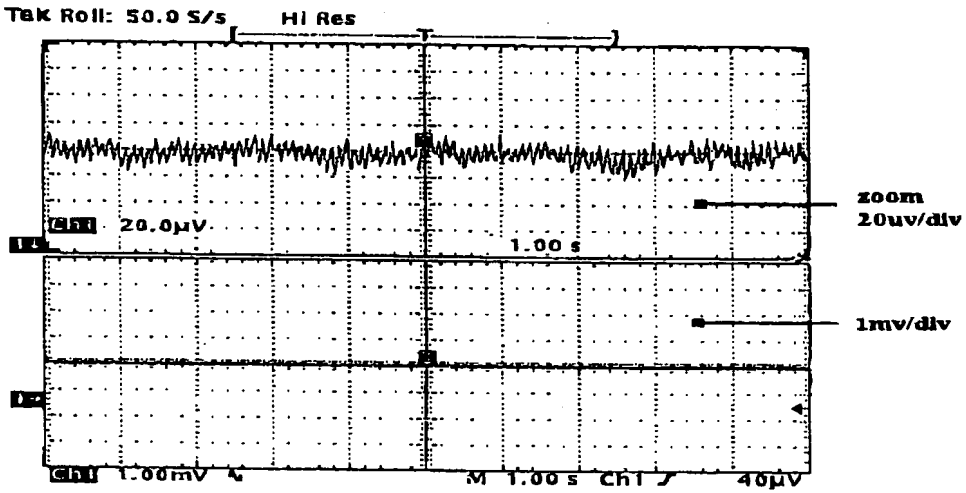

Tek Roll: 50.0 S/s
Hi Res
20.0µV
1.00 s
zoom
20uv/div
1mv/div
Ch1 1.00mV
M 1.00 s Ch1
40µV

Figure 20

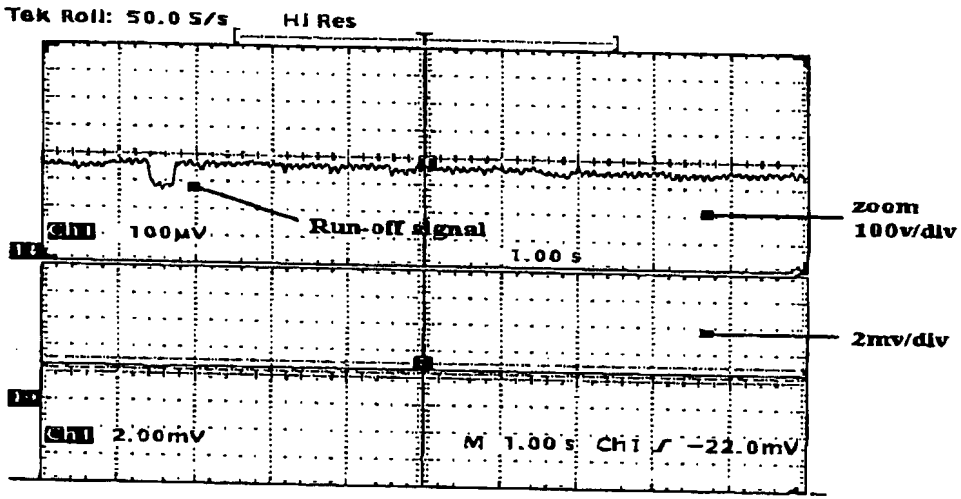

Tek Roll: 50.0 S/s
Hi Res
Run-off signal
zoom
100v/div
Ch1 100µV
1.00 s
2mv/div
Ch1 2.00mV
M 1.00 s Ch1 ƒ -22.0mV

Figure 21

Figure 22